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Drug-Associated Acute Pancreatitis: Twenty-one Years of Spontaneous Reporting in the Netherlands

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OBJECTIVE: Drugs are considered a rare cause of acute pancreatitis. We conducted a descriptive study to assess which drugs have been associated with acute pancreatitis in spontaneous adverse drug reaction reports in the Netherlands.

METHODS: Our study is based on reports of drug-associated acute pancreatitis reported to the Netherlands Center for Monitoring of Adverse Reactions to Drugs and the Netherlands Pharmacovigilance Foundation LAREB between 1 January 1977 and 1 January 1998. We used an algorithm to validate the diagnosis and to assess the causal relationship between acute pancreatitis and use of the suspected drug.

RESULTS: A total of 55 cases were available for review. We excluded 11 (20.0%) reports, as we could not confirm the diagnosis of acute pancreatitis. Another 10 (18%) cases were excluded, as the causal relationship with the suspected drug was unlikely. In the remaining 34 reports, acute pancreatitis was labeled as definite in 11 (32%) and as probable in 23 (68%). The age of the patients ranged from 17 to 84 yr with a median of 41; 24 (71%) patients were female. Of the 34 cases, 27 (79%) recovered, five (15%) died, and in two (6%) the outcome is unknown. Azathioprine, cimetidine, interferon-α, methyldopa, metronidazole, olsalazine, and oxyphenbutazon all had a definite causal relationship with acute pancreatitis. Doxycycline, enalapril, famotidine, ibuprofen, maprotiline, mesalazine, and sulindac had a probable causal relationship with acute pancreatitis.

CONCLUSIONS: A variety of drugs was associated with acute pancreatitis in Dutch adverse drug reaction reports. Quantitative information about drug-induced pancreatitis is scanty. Epidemiological studies to assess the risk of drug-induced acute pancreas, therefore, are needed. (Am J Gastroenterol 1999;94:2417–2422. © 1999 by Am. Coll. of Gastroenterology)

INTRODUCTION

Acute pancreatitis is a severe disease with considerable morbidity and mortality. The incidence of acute pancreatitis seems to be rising in Western countries (1–5). Despite advanced critical care, the case-fatality proportion remains around 5–10% (1, 3, 6, 7). Gallstones and alcohol consumption are the most important risk factors for acute pancreatitis (8–10). Other risk factors include hyperlipidemia, hypercalcemia, endoscopic retrograde cholangiopancreatography (ERCP), and trauma. In 10–25% of the patients with acute pancreatitis, no obvious risk factors are present.

Drugs are rarely associated with the occurrence of acute pancreatitis (11–14). The pathogenesis of drug-induced acute pancreatitis has not yet been clarified.

The spontaneous adverse reaction-reporting scheme has been in operation since the early 1960s in the Netherlands. From 1977 until 1998 the Netherlands Center for Monitoring of Adverse Reactions to Drugs of the Inspectorate for Health Care and the Netherlands Pharmacovigilance Foundation LAREB received 55 spontaneous reports of possible drug-induced acute pancreatitis. We conducted a descriptive study to assess which drugs were associated with acute pancreatitis in Dutch adverse drug reaction (ADR) reports.

MATERIALS AND METHODS

All reports of drug-associated acute pancreatitis reported to the Netherlands Center for Monitoring of Adverse Reactions to Drugs and the Netherlands Pharmacovigilance Foundation LAREB between 1 January 1977 and 1 January 1998 were independently reviewed by two of the authors (I.A., E.P.), as to the probability of the diagnosis of acute pancreatitis and as to the likelihood of a causal relationship with the suspected drug. Discrepancies were discussed in a consensus meeting (I.A., E.P., B.H.Ch.). Agreement was reached on all reports.

The diagnosis of acute pancreatitis was labeled as definite when acute pancreatitis was confirmed by computed tomography (CT), laparotomy, or autopsy. The diagnosis was also considered definite when positive findings on ultrasound were combined with abdominal pain and an elevated level of serum amylase or lipase. Acute pancreatitis was labeled as probable when two of the following three criteria were

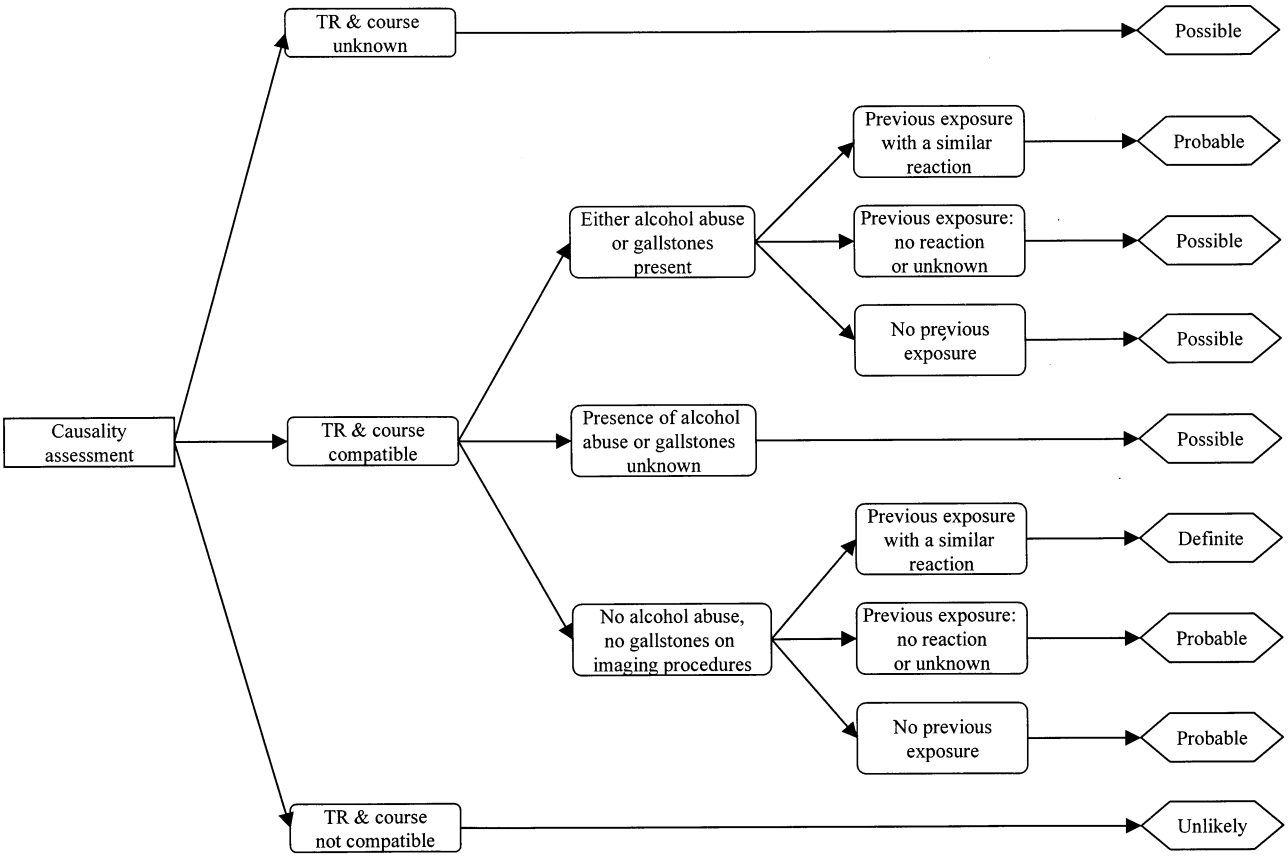

Figure 1. Drug-associated acute pancreatitis: assessment of a causal relationship with the suspected drug in the absence of rechallenge data. TR, time relationship between first intake of the drug and onset of acute pancreatitis.

present: 1) positive findings on ultrasound examination, 2) abdominal pain, and 3) elevated serum amylase or lipase. We defined a swollen or enlarged pancreas, an indistinct or vaguely bordered pancreas, peripancreatic fat infiltration, and necrosis of the pancreas on CT or ultrasound examination as positive signs of acute pancreatitis. Cases were excluded if the above-mentioned criteria were not met or if signs of chronic pancreatitis were found at ERCP, surgery, or autopsy. We defined pancreatic calcifications or an irregular pancreatic duct as signs of chronic pancreatitis.

The causal relationship between acute pancreatitis and the suspected drug was assessed according to Figure 1 if no data on rechallenge were provided. The causal relationship was classified as *possible* when other risk factors for acute pancreatitis were present, or when the presence of gallstones or alcohol abuse (>5 units per day) was not known. In patients with a relapse of acute pancreatitis after rechallenge, the causal relationship was considered *definite*.

RESULTS

From 1977 until 1998, the Netherlands Center for Monitoring of Adverse Reactions to Drugs received 45 reports and the LAREB Netherlands Pharmacovigilance Foundation received 13 reports of drug-associated acute pancreatitis. Three of the 58 reports were reported to both reporting centers, leaving 55 episodes of suspected drug-induced acute pancreatitis.

Eleven (20%) reports were excluded, as we could not confirm the diagnosis of acute pancreatitis. In six cases, the criteria for definite or probable acute pancreatitis were not met, and five cases concerned chronic pancreatitis. In 10 (18%) cases the causal relationship between the suspected drug and the occurrence of acute pancreatitis was labeled unlikely because of an incompatible time relationship between start of drug treatment and development of acute pancreatitis or because of a relapse after discontinuation of the drug. These cases were excluded from the analysis.

In the remaining 34 case-histories, the diagnosis of acute pancreatitis was considered definite in 11 (32%) and probable in 23 (68%) cases. A discharge summary could be obtained for 33 of these 34 (97%) adverse drug reaction reports. The remaining report had enough clinical data for a reliable assessment. The data concerned 24 (71%) women and 10 (29%) men. Age ranged from 17 to 84 yr, with a median of 41 yr. Twenty-seven patients (79%) were admitted with abdominal pain, three (9%) were admitted with back pain, and in four (12%), the symptoms on admission were unknown. Thirty-two patients (94%) had an elevated

Table 1. Characteristics of 34 Reports of Drug-Associated Acute Pancreatitis

Sex	Age	Drug	Dose (*)	TR	Gallst.	Alc. Abuse	CR	Outc.	Remarks
F	33	alendronate	10 mg	21 days	yes	?	possible	†	
F	42	azathioprine	50 mg	10 days	no	?	definite	rec.	rechallenge+
F	58	azathioprine	75 mg	19 days	no	?	definite	rec.	rechallenge+
F	39	azathioprine	50 mg	25 days	no	no	probable	rec.	
F	27	azathioprine	100 mg	15 days	?	?	possible	rec.	
F	57	captopril	50 mg	2 years	no	no	possible	rec.	treatment was continued, another attack after 18 months
M	67	ciclosporine/ isradipine	?	59 days	no	no	possible	†	acute pancreatitis after kidney transplantation
M	38	cimetidine	800 mg	5 days	no	no	definite	rec.	developed acute pancreatitis after cimetidine 9 yr ago
F	67	ciprofibrate	100 mg	23 days	?	no	possible	†	ciprofibrate for hyperlipidemia
M	59	didanosine	400 mg	95 days	no	?	possible	†	HIV+
M	23	doxycycline	100 mg	1 day	no	no	probable	rec.	
M	60	enalapril	5 mg	96 days	no	no	probable	rec.	inadequate rechallenge
M	62	famotidine	20 mg	some months	no	no	probable	†	
F	25	ibuprofen	3600 mg	10 days	no	no	probable	rec.	up to 8 tablets (600 mg) a day
M	40	interferon-α	3 MU t.i.w.	15 wk	no	5E/day	definite	rec.	rechallenge+
F	59	jotrolan	?	6 h	?	?	possible	?	contrast agent used at ERCP, 800 mg of gentamycine was added to the contrast agent
F	84	jotrolan	?	4 h	yes	?	possible	?	contrast agent used at ERCP, 800 mg of gentamycine was added to the contrast agent
F	27	lamivudine	300 mg	206 days	no	?	possible	rec.	HIV+
F	46	maprotiline	75 mg	10 days	no	no	probable	rec.	
F	26	mesalazine‡	3000 mg	16 days	no	no	probable	rec.	azathioprine-induced acute pancreatitis 4 months later
M	36	mesalazine‡	1500 mg	7 days	no	no	probable	rec.	
F	31	mesalazine‡	3000 mg	28 days	no	no	probable	rec.	
F	23	mesalazine	1500 mg	8 days	?	no	possible	rec.	
F	61	methyldopa‡	?	14 days	no	?	definite	rec.	rechallenge+
F	69	methyldopa‡	500 mg	14 days	yes	?	definite	rec.	rechallenge+
F	73	metronidazole/ tetracycline/ bismuth	1500 mg 2000 mg 480 mg	1 day	no	?	possible	rec.	history of carcinoma ampulla Vateri
F	46	metronidazole‡	2000 mg	1 day	no	no	definite	rec.	4 and 7 years ago acute pancreatitis after metronidazole
M	34	nelfinavir/ nevirapine/ AZT	1000 mg 200 mg 200 mg	22 days	no	?	possible	rec.	HIV+, CMV+, cryptosporidium+
F	23	olsalazine‡	1500 mg	5 days	no	no	definite	rec.	rechallenge+
F	32	oxyphenbutaz‡	200 mg	21 days	no	no	definite	rec.	rechallenge+
F	27	propyfenazon/ paracetamol/ coffeinum	?	?	no	?	possible	rec.	had an attack of acute pancreatitis 4 months earlier
M	57	sulindac	800 mg	1 month	no	no	probable	rec.	3 attacks of acute pancreatitis during 15 months of treatment
F	66	sulindac/ergotamine	?	?	no	no	possible	rec.	
F	17	tetracycline	750 mg	8 days	no	?	possible	rec.	mumps virus+

TR = time relationship between first intake of the drug and onset of acute pancreatitis; gallst = gallstones; alc. abuse = alcohol abuse; CR = causal relationship between the suspected drug and acute pancreatitis; outc = outcome; ? = unknown; rec. = recovered.
* per day; † died; ‡ have been reported in case reports.

level of serum amylase or lipase, one (3%) had a normal level of serum amylase, and in 1 patient (3%) no enzyme levels were mentioned. CT scanning and US examination revealed signs of acute pancreatitis in 7 and 9 cases, respectively.

The causal relationship with the suspected drug was considered definite in 9 cases (26%), probable in 10 (29%), and possible in 15 (44%). Table 1 lists patient characteristics, other risk factors for acute pancreatitis, the time and causal relationship between drug intake and

development of symptoms, and the outcomes in our 34 patients.

DISCUSSION

In this case series, we evaluated 55 Dutch reports of drug-associated acute pancreatitis which yielded 14 drugs with a probable or definite association with the outcome: azathioprine, cimetidine, doxycycline, enalapril, famotidine, ibuprofen, interferon-α, maprotiline, mesalazine, methyldopa, metronidazole, olsalazine, oxyphenbutazon and sulindac. To our knowledge maprotiline and famotidine have not previously been reported to be associated with acute pancreatitis.

Most of the "evidence" of associations between drugs and acute pancreatitis is based on anecdotal case-reports. Reviews most frequently mention aminosalicylates, L-asparginase, estrogens, thiazide diuretics, valproate, azathioprine, corticosteroids, furosemide, mercaptopurine, tetracycline, sulindac, and pentamidine (11–14). The World Health Organization (WHO) has received a total of 2749 reports of drug-associated acute pancreatitis in the period between 1968 and 1993. ACE inhibitors (n = 209), valproate (n = 219), H2-receptor-blockers (n = 127), sulindac (n = 121), azathioprine (n = 73), gemfibrozil (n = 72), lovastatin (n = 72), pentamidine (n = 62), and didanosine (n = 61) were the most frequently reported drugs (15).

Despite this relatively large volume of case-based evidence, surprisingly little is known about the epidemiology (incidence and relative risks) and mechanisms of drug-associated pancreatitis. Epidemiological evidence is limited to two small case-control studies that have shown an increased risk of acute pancreatitis associated with use of diuretics (16, 17).

It is well known that the incidence of an adverse effect cannot validly be estimated from spontaneous reports. This is due to large underreporting to voluntary reporting schemes, and the scantiness of information on spontaneous reports, which complicates validation of the outcome and assessment of causality to the suspected drugs. To facilitate validation and causality assessment in our case series, we collected additional clinical information. Causality assessment was based on the temporal relationship, effect of dechallenge, rechallenge, and the presence of other established causes (*e.g.*, gallstones, excessive alcohol intake, ERCP). Although our assessments were based on retrospective review of discharge summaries that may lack information on the presence of risk factors, we excluded 11 of 55 cases on the basis of an uncertain diagnosis, and another 10 were excluded because a causal relationship was unlikely. This shows that thorough evaluation of spontaneous reports is, indeed, necessary before making inferences on any kind of frequency or association.

The mechanism of drug-induced pancreatitis is largely unknown. In general, characteristics of the adverse event such as the temporal relationship, dose response, dechallenge, and rechallenge may help in suggesting potential mechanisms. For instance, mesalazine may possibly provoke immunological damage to the pancreas, as rechallenge with small doses can induce relapses of acute pancreatitis within hours (18–32). However, one should be careful associating these drugs with acute pancreatitis, as inflammatory bowel disease itself may also cause pancreatitis (33–37). The same argument holds for azathioprine. This drug has often been associated with pancreatitis, even with positive rechallenge (38–43), but other studies could not confirm this association (44–46).

Localized angioedema with obstruction of the pancreatic duct may be the mechanism by which ACE inhibitors cause acute pancreatitis (47). Time intervals between the start of ACE inhibitor treatment and the onset of acute pancreatitis vary between 1 day and 2 yr (47–55). These intervals are consistent with induction times described for ACE inhibitor–induced angioedema (56–58).

Protopathic bias (prescription of a drug for prodromal symptoms of the outcome) may explain the reports regarding use of H2-blockers and acute pancreatitis (59–61). An argument in favor of a real association is the positive rechallenge that we and others have observed after the readministration of cimetidine (60). If true, the mechanism remains unknown, but the rapid relapse within 24 h after re-exposure suggests an idiosyncratic reaction. As compared to cimetidine, famotidine is a relatively new H2-blocker, which may explain why we are the first to report an association between this drug and acute pancreatitis. However, previous considerations regarding a potential protopathic bias are equally valid for this H2-blocking agent.

Reports of NSAID-induced acute pancreatitis are sparse, as are hypotheses on a possible biological mechanism (62–68). Sulindac seems to stand out, followed by oxyphenbutazon (69–82). One report has been published on a patient who developed possible acute pancreatitis as part of a generalized hypersensitivity syndrome to ibuprofen (83). However, this patient also had parotitis, which may explain the hyperamylasemia and systemic lupus erythematosus which, in itself, may be a risk factor for acute pancreatitis (8). As for H2-blockers, the association between NSAID use and acute pancreatitis may be explained by protopathic bias, inasmuch as analgesics may be used for abdominal pain.

One case has been described previously of a 9-yr-old girl who developed acute pancreatitis after 14 months of treatment with interferon-α for chronic myelogenous leukemia (84). In our case series, we described one patient with a recurrence of acute pancreatitis after readministration of interferon-α, which makes a causal association likely.

Our two reports of methyldopa-associated pancreatitis are consistent with one case that has been published previously (85). All three patients experienced a positive rechallenge reaction, within hours after rechallenge, which suggests an idiosyncratic reaction (85–87).

The association between metronidazole and acute pancreatitis remains unclear. No mechanism is known, but five

reports have suggested a possible association (88–92). However, a cohort study among 6485 users of metronidazole did not yield one hospitalization for acute pancreatitis (93).

In conclusion, a wide variety of different drugs was associated with acute pancreatitis in our Dutch case series. Most of the drugs have been associated with acute pancreatitis before; however, acute pancreatitis due to famotidine and maprotiline has not been reported before. Despite numerous case reports on drug-induced acute pancreatitis, quantitative information on this subject is scanty. Large scale epidemiological studies are necessary to assess the risk of drug-induced acute pancreatitis.

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REFERENCES

1. Jaakkola M, Nordback I. Pancreatitis in Finland between 1970 and 1989. Gut 1993;34:1255–60.
2. Wilson C, Imrie CW. Changing patterns of incidence and mortality from acute pancreatitis in Scotland, 1961–1985. Br J Surg 1990;77:731–4.
3. Lankisch PG, Schirren CA, Schmidt H, et al. Etiology and incidence of acute pancreatitis: A 20-year study in a single institution. Digestion 1989;44:20–5.
4. Katschinski BD, Giggs JA, Bourke JB. Inzidenz und geographische Verteilung der akuten Pankreatitis in Nottingham von 1969 bis 1983. Z Gastroenterol 1990;28:183–7.
5. Corfield AP, Cooper MJ, Williamson RC, et al. Prediction of severity in acute pancreatitis: Prospective comparison of three prognostic indices. Lancet 1985;2:403–7.
6. Mann DV, Hershman MJ, Hittinger R, et al. Multicentre audit of death from acute pancreatitis. Br J Surg 1994;81:890–3.
7. Amurawaiye EO, Brown RA. Acute pancreatitis—30 Years' experience at a teaching hospital. Can J Surg 1991;34:137–43.
8. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med 1994;330:1198–210.
9. Marshall JB. Acute pancreatitis. A review with an emphasis on new developments. Arch Intern Med 1993;153:1185–98.
10. Thomson SR, Hendry WS, McFarlane GA, et al. Epidemiology and outcome of acute pancreatitis. Br J Surg 1987;74: 398–401.
11. Banerjee AK, Patel KJ, Grainger SL. Drug-induced acute pancreatitis. A critical review. Med Toxicol Adverse Drug Exp 1989;4:186–98.
12. Frick TW, Speiser DE, Bimmler D, et al. Drug-induced acute pancreatitis: Further criticism. Dig Dis 1993;11:113–32.
13. Mallory A, Kern F. Drug-induced pancreatitis. Baillieres Clin Gastroenterol 1988;2:293–307.
14. Wilmink T, Frick TW. Drug-induced pancreatitis. Drug Safety 1996;14:406–23.
15. Bergholm U, Langman M, Rawlins M, et al. Drug-induced acute pancreatitis. Pharmacoepidemiol Drug Safety 1995;4: 329–34.
16. Moir DC. Drug-associated acute pancreatitis. Lancet 1978;2: 369–70.
17. Bourke JB, McIllmurray MB, Mead GM, et al. Drug-associated primary acute pancreatitis. Lancet 1978;1:706–8.
18. Poldermans D, van Blankenstein M. Pancreatitis induced by disodium azodisalicylate. Am J Gastroenterol 1988;83:578–80.
19. Deprez P, Descamps C, Fiasse R. Pancreatitis induced by 5-aminosalicylic acid. Lancet 1989;2:445–6.
20. Grimaud JC, Maillot A, Bremondy A, et al. Faut-il toujours accuser la sulfapyridine? A propos d'un cas de pancreatite aigue induite par la mesalazine. Gastroenterol Clin Biol 1989; 13:432.
21. Sachedina B, Saibil F, Cohen LB, et al. Acute pancreatitis due to 5-aminosalicylate. Ann Intern Med 1989;110:490–2.
22. Fiorentini MT, Fracchia M, Galatola G, et al. Acute pancreatitis during oral 5-aminosalicylic acid therapy. Dig Dis Sci 1990;35:1180–2.
23. Isaacs KL, Murphy D. Pancreatitis after rectal administration of 5-aminosalicylic acid. J Clin Gastroenterol 1990;12:198–9.
24. Eckardt VF, Kanzler G, Rieder H, et al. 5-Aminosalicylsaure-assoziierte Pankreatitis. Dtsch Med Wochenschr 1991;116: 540–2.
25. Tran K, Froguel E, Jian R, et al. Acute pancreatitis induced by mesalazine. J Clin Gastroenterol 1991;13:715–6.
26. Besseau M, Delchier JC, Blazquez M, et al. Pancreatite aiguë a la mesalazine. Gastroenterol Clin Biol 1991;15:174.
27. Hochain P, Guedon C, Colin R. Pancreatite aiguë au cours d'une maladie de Crohn traitée par mesalazine orale. Gastroenterol Clin Biol 1991;15:173.
28. Tromm A, May B. 5-Aminosalicylsaure-assoziierte Pankreatitis. Dtsch Med Wochenschr 1991;116:1125.
29. Erdkamp F, Houben M, Ackerman E, et al. Pancreatitis induced by mesalamine. Neth J Med 1992;41:71–3.
30. Radke M, Bartolomaeus G, Muller M, et al. Acute pancreatitis in Crohn's disease due to 5-ASA therapy. J Pediatr Gastroenterol Nutr 1993;16:337–9.
31. Debongnie JC, Dekoninck X. Sulfasalazine, 5-ASA and acute pancreatitis in Crohn's disease. J Clin Gastroenterol 1994;19: 348–9.
32. Eland I, De Gooyer D, Stokkers P, et al. Acute pancreatitis toegeschreven aan het gebruik van mesalazine. Tijdschr Geneeskd 1998;54:417–20.
33. Seyrig JA, Jian R, Modigliani R, et al. Idiopathic pancreatitis associated with inflammatory bowel disease. Dig Dis Sci 1985;30:1121–6.
34. Niemela S, Lehtola J, Karttunen T, et al. Pancreatitis in patients with chronic inflammatory bowel disease. Hepatogastroenterology 1989;36:175–7.
35. Tromm A, Huppe D, Micklefield GH, et al. Acute pancreatitis complicating Crohn's disease: Mere coincidence or causality? Gut 1992;33:1289–91.
36. Eisner TD, Goldman IS, McKinley MJ. Crohn's disease and pancreatitis. Am J Gastroenterol 1993;88:583–6.
37. Weber P, Seibold F, Jenss H. Acute pancreatitis in Crohn's disease. J Clin Gastroenterol 1993;17:286–91.
38. Nogueira JR, Freedman MA. Acute pancreatitis as a complication of Imuran therapy in regional enteritis. Gastroenterology 1972;62:1040–1.
39. Kawanishi H, Rudolph E, Bull FE. Azathioprine-induced acute pancreatitis. N Engl J Med 1973;289:357.

40. Paloyan D, Levin B, Simonowitz D. Azathioprine-associated acute pancreatitis. Am J Dig Dis 1977;22:839–40.
41. Isenberg JN. Pancreatitis, amylase clearance, and azathioprine. J Pediatr 1978;93:1043–4.
42. Guillaume P, Grandjean E, Male PJ. Azathioprine-associated acute pancreatitis in the course of chronic active hepatitis. Dig Dis Sci 1984;29:78–9.
43. Major GA, Moore PG. Profound circulatory collapse due to azathioprine. J R Soc Med 1985;78:1052–3.
44. Frick TW, Fryd DS, Goodale RL, et al. Lack of association between azathioprine and acute pancreatitis in renal transplantation patients. Lancet 1991;337:251–2.
45. Broe PJ, Cameron JL. Azathioprine and acute pancreatitis: Studies with an isolated perfused canine pancreas. J Surg Res 1983;34:159–63.
46. Dreiling DA, Nacchiero M. The effect of Imuran on pancreatic secretion. A preliminary report. Am J Gastroenterol 1978;69: 491–3.
47. Maringhini A, Termini A, Patti R, et al. Enalapril-associated acute pancreatitis: Recurrence after rechallenge. Am J Gastroenterol 1997;92:166–7.
48. Tilkemeier P, Thompson PD. Acute pancreatitis possibly related to enalapril. N Engl J Med 1988;318:1275–6.
49. Roush MK, McNutt RA, Gray TF. The adverse effect dilemma: Quest for accessible information. Ann Intern Med 1991;114:298–9.
50. Pedro-Botet J, Miralles R, Coll J, et al. Captopril versus enalapril: Cough versus pancreatitis. DICP 1990;24:438–9.
51. Dabaghi S. ACE inhibitors and pancreatitis. Ann Intern Med 1991;115:330–1.
52. Martin T, Taupignon A, Graf E, et al. Pancreatite et hepatite chez une femme traitée par maleate d'enalapril. Un cas. Therapie 1989;44:449–50.
53. Gonzalez Ramallo VJ, Muino Miguez A, Torres Segovia FJ. Necrotizing pancreatitis and enalapril. Eur J Med 1992;1:123.
54. Standridge JB. Fulminant pancreatitis associated with lisinopril therapy. South Med J 1994;87:179–81.
55. Maliekal J, Drake CF. Acute pancreatitis associated with the use of lisinopril. Ann Pharmacother 1993;27:1465–6.
56. Sabroe RA, Black AK. Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. Br J Dermatol 1997;136: 153–8.
57. O'Mara N, O'Mara E Jr. Delayed onset of angioedema with angiotensin-converting enzyme inhibitors: Case report and review of the literature. Pharmacotherapy 1996;16:675–9.
58. Forslund T, Tohmo H, Weckstrom G, et al. Angio-oedema induced by enalapril. J Intern Med 1995;238:179–81.
59. Arnold F, Doyle PJ, Bell G. Acute pancreatitis in a patient treated with cimetidine. Lancet 1978;1:382–3.
60. Wilkinson ML, O'Driscoll R, Kiernan TJ. Cimetidine and pancreatitis. Lancet 1981;1:610–1.
61. Nott DM, de Sousa BA. Suspected cimetidine-induced acute pancreatitis. Br J Clin Pract 1989;43:264–5.
62. Jick H, Derby LE, Garcia Rodriguez LA, et al. Nonsteroidal antiinflammatory drugs and certain rare, serious adverse events: A cohort study. Pharmacotherapy 1993;13:212–7.
63. Guerra M. Toxicity of indomethacin. Report of a case of acute pancreatitis. JAMA 1967;200:552–3.
64. Cobb TK, Pierce JR Jr. Acute pancreatitis associated with ketoprofen. South Med J 1992;85:430–1.
65. Khan IH, Edward N. Pancreatitis associated with diclofenac. Postgrad Med J 1993;69:486–7.
66. Du Ville L, Debeuckelaere S, Reynaert H, et al. Pancreatitis associated with naproxen. Am J Gastroenterol 1993;88:464.
67. Castiella A, Lopez P, Bujanda L, et al. Possible association of acute pancreatitis with naproxen. J Clin Gastroenterol 1995; 21:258.
68. Van Walraven AA, Edels M, Fong S. Pancreatitis caused by mefenamic acid. Can Med Assoc J 1982;126:894.
69. Goldstein J, Laskin DA, Ginsberg GH. Sulindac associated with pancreatitis. Ann Intern Med 1980;93:151.
70. Siefkin AD. Sulindac and pancreatitis. Ann Intern Med 1980; 93:932–3.
71. Memon AN. Pancreatitis and sulindac. Ann Intern Med 1982; 97:139.
72. Lilly EL. Pancreatitis after administration of sulindac. JAMA 1981;246:2680.
73. Klein SM, Khan MA. Hepatitis, toxic epidermal necrolysis and pancreatitis in association with sulindac therapy. J Rheumatol 1983;10:512–3.
74. Clark BG, Vestal RE. Adverse drug reactions in the elderly: Case studies. Geriatrics 1984;39:53–4, 60–3, 66.
75. Detlefs RL. Drug-induced pancreatitis presenting as subcutaneous fat necrosis. J Am Acad Dermatol 1985;13:305–7.
76. Zygmunt DJ, Williams HJ, Bienz SR. Acute pancreatitis associated with long-term sulindac therapy. West J Med 1986; 144:461–2.
77. Lerche A, Vyberg M, Kirkegaard E. Acute cholangitis and pancreatitis associated with sulindac (Clinoril). Histopathology 1987;11:647–53.
78. Sugerman HJ. Sulindac-induced acute pancreatitis mimicking gallstone pancreatitis. Am Surg 1989;55:536–8.
79. Anonymous. Oxifenbutazon (Tanderil) och pankreatit. Lakartidningen 1972;69:3088.
80. Kristensson H. Oxifenbutazonutlost pankreatit—Ospecifik GT-stegring. Lakartidningen 1982;79:3463.
81. Versteegh MI, Vijverberg PL, van Dijk HA. Pancreasprikkeling door oxyfenbutazon (Tanderil). Ned Tijdschr Geneeskd 1983;127:1924–5.
82. Bosch JA, Valdes M, Oristrell J, et al. Oxyphenbutazone-induced sialadenitis, intrahepatic cholestasis and pancreatitis. Acta Gastroenterol Belg 1985;48:529–30.
83. Ruppert GB, Barth WF. Ibuprofen hypersensitivity in systemic lupus erythematosus. South Med J 1981;74:241–3.
84. Sotomatsu M, Shimoda M, Ogawa C, et al. Acute pancreatitis associated with interferon-alpha therapy for chronic myelogenous leukemia. Am J Hematol 1995;48:211–2.
85. Rominger JM, Gutierrez JG, Curtis D, et al. Methyldopa-induced pancreatitis. Am J Dig Dis 1978;23:756–8.
86. Warren SE, Mitas JA, Swerdlin AH. Pancreatitis due to methyldopa: Case report. Mil Med 1980;145:399–400.
87. Van der Heide H, Ten Haaft MA, Stricker BH. Pancreatitis caused by methyldopa. Br Med J (Clin Res Ed) 1981;282: 1930–1.
88. Plotnick BH, Cohen I, Tsang T, et al. Metronidazole-induced pancreatitis. Ann Intern Med 1985;103:891–2.
89. Sanford KA, Mayle JE, Dean HA, et al. Metronidazole-associated pancreatitis. Ann Intern Med 1988;109:756–7.
90. Celifarco A, Warschauer C, Burakoff R. Metronidazole-induced pancreatitis. Am J Gastroenterol 1989;84:958–60.
91. Corey WA, Doebbeling BN, DeJong KJ, et al. Metronidazole-induced acute pancreatitis. Rev Infect Dis 1991;13:1213–5.
92. de Jongh FE, Ottervanger JP, Stuiver PC. Acute pancreatitis door metronidazol. Ned Tijdschr Geneeskd 1996;140:37–8.
93. Friedman GD, Selby JV. How often does metronidazole induce pancreatitis? Gastroenterology 1990;98:1702–3.